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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Mezher H. Ali et al.

Application No.: Not Yet Assigned

Confirmation No.: N/A

Filed: Concurrently Herewith

Art Unit: N/A

For: PIPERIDINETRIOL DERIVATIVES AS
INHIBITORS OF GLYCOSYLCERAMID
SYNTHASE

Examiner: Not Yet Assigned

AFFIRMATION OF PRIORITY CLAIM

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Applicant hereby claims priority under 35 U.S.C. 119 based on the following prior foreign applications filed in the following foreign country on the dates indicated:

Country	Application No.	Date
Great Britain	0216656.9	July 17, 2002
Great Britain	0301480.0	January 22, 2003
Great Britain	0313674.8	June 13, 2003

Certified copies of the aforesaid Patent Applications were received by the International Bureau on October 31, 2003 during the pendency of International Application No. PCT/GB03/03244. A copy of Form PCT/IB/304 is enclosed.

Dated: January 13, 2005

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PCT/GB 2003 / 003244



PRIORITY DOCUMENT

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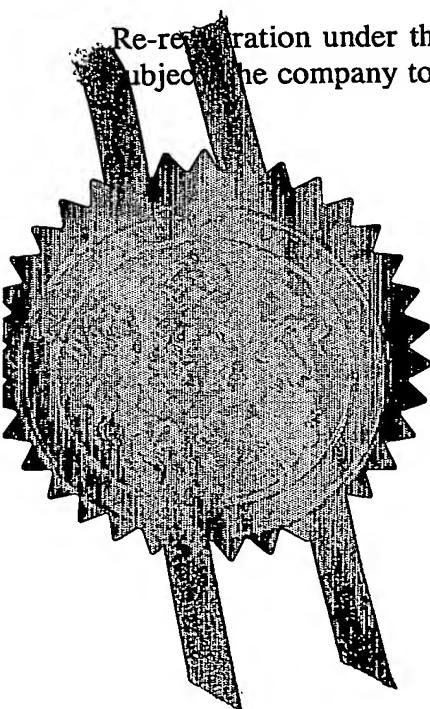
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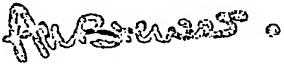
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NOVEL COMPOUNDS

The present invention relates to novel piperidine derivatives useful as inhibitors of glucosylceramide synthase (GCS; UDP-glucose:ceramide glycosyltransferase UDP-glucose:N-5 acylsphingosine D-glycosyltransferase, EC 2.4.1.80), methods for their preparation and their use in medicine, specifically in the treatment and prevention of disease states mediated by GCS. The compounds find use in the treatment of glycolipid storage diseases, diseases associated with glycolipid accumulation, cancers in which glycolipid synthesis is abnormal, infectious diseases caused by organisms which use cell surface glycolipids as receptors, 10 infectious diseases in which synthesis of glucosylceramide is essential or important, diseases in which excessive glycolipid synthesis occurs, neuronal disorders and neuronal injury. Their synthesis is also described, as are pharmaceutical formulations comprising the compounds and methods of treatment using the compounds.

GCS is an intracellular enzyme that catalyzes the assembly of uridine diphosphate-glucose and ceramide into the glycolipid, glucosylceramide. GCS's role in biology is 15 currently the subject of intense basic and applied science interest. For example, many investigators are exploring the role of GCS in regulating ceramide levels since this molecule can induce apoptotic cell death (J. Biol. Chem., 2000, Mar 10, 275(10), 7138-43). Similarly, there is active research into the role of GCS in maintaining cholesterol/glycolipid 'rafts,' cell-20 surface membrane domains of specialized permeability and functionality that appear to be involved in a variety of signal transduction events (Nature, 1997, Jun 5, 387(6633), 569-72).

GCS also is a target for treating certain human diseases. Glucosylceramide and structurally related glycolipids are stored in the lysosomes of patients with genetic diseases which result from a mutation in one of the essential glycolipid-degrading enzymes (e.g., 25 Gaucher, Tay Sachs, Sandhoff, GM1 gangliosidosis and Fabry diseases). Glycolipid storage also occurs as a secondary effect in some tissues (e.g., neuronal tissue) with genetic storage diseases such as Niemann-Pick C disease, mucopolysaccharidoses, mucolipidosis type IV (Proc. Natl. Acad. Sci. USA, 1998, May 26, 95(11), 6373-8) and α -mannosidosis (Proc. Natl. Acad. Sci. USA, 1991 Dec 15, 88(24), 11330-4). It has been reasoned that GCS inhibitors 30 may be applied to reduce the rate of glycolipid synthesis in diseased cells so that there is less glycolipid present to be stored, a treatment approach termed substrate deprivation. Studies have demonstrated that GCS inhibitors can in fact be used to reduce the glycolipid accumulation seen in cell and animal models of glycolipid storage (Proc. Natl. Acad. Sci. USA, 1999, May 25, 96(11), 6388-93; Science, 1997, Apr 18, 276(5311), 428-31; J. Clin. 35 Invest., 2000, Jun, 105(11), 1563-71). Furthermore, a recent clinical trial report has shown that GCS inhibitors such as N-butyldeoxynojirimycin (NB-DNJ) are useful in treating human patients with Gaucher disease (Lancet, 2000, Apr 29, 355(9214), 1481-5). The use of the imino sugar NB-DNJ as a GCS inhibitor is disclosed in EP-A-0698012. EP-A-0536402 and EP-A-0698012 disclose that N-alkyl derivatives of deoxygalactonojirimycin, e.g. N-40 butyldeoxygalactonojirimycin (NB-DGJ), may also be of use in the treatment of glycolipid storage disorders. EP-A-0698012 also discloses that the corresponding N-butyl derivatives of mannose (NB-DMJ), fucose (NB-DFJ) and N-acetylglucosamine (NB-NAG) do not act as inhibitors of glycolipid biosynthesis.

The use of GCS inhibitors in the treatment of human malignancies has been proposed. Tumours can synthesize abnormal quantities of glycolipids and/or glycolipids not present in the normal tissue. In addition glycolipids or gangliosides in particular are shed by tumour cells and released into the extracellular space and the bloodstream. Both tumour shed and cell surface bound tumour gangliosides can influence tumour host cell interactions such as cell-cell contacts or adhesion (Methods Enzymol., 2000, 312, 447-58), cell motility (Mol. Chem. Neuropathol., 1995 Feb-Apr, 24(2-3), 121-35), growth factor signalling events (J. Biol. Chem., 2000 Nov 3, 275(44), 34213-23), tumour stimulated angiogenesis (Acta. Oncol., 1997, 36(4), 383-7) and tumour specific immune responses (J. Immunol., 1999 Oct 1, 163(7), 3718-26). All these events can affect tumour development and progression. Glycolipids, glucosylceramide in particular, are known to accumulate in multidrug resistant (MDR) tumour cells (Anticancer Res., 1998 Jan-Feb, 18(1B), 475-80) and in vitro treatment of these cells with GCS inhibitors can reverse the MDR phenotype (J. Biol. Chem., 1997, Jan 17, 272(3), 1682-7; Br. J. Cancer, 1999, Oct, 81(3), 423-30).

Cell surface glycolipids also have roles in infectious disease, serving as receptors for the binding of pathogenic bacteria (APMIS, 1990, Dec, 98(12), 1053-60, Review), fungi (Infect. Immun., 1990 Jul, 58(7), 2085-90) and viruses (FEBS Lett., 1984 May 7, 170(1), 15-8). In addition, glycolipids on the surface of cells are bound by bacterial toxins (Methods Enzymol., 2000, 312, 459-73) for instance the B subunit of cholera toxin (ganglioside GM1) and verocytotoxin (globotriaosylceramide GB3) (J. Infect. Dis., 2001, suppl. 70-73, 183).

The use of GCS inhibitors may also be appropriate in a number of other clinical indications which are associated with abnormalities in glycolipid synthesis. Atherosclerotic lesions of human aorta have a higher ganglioside content than unaffected regions of the aorta and serum ganglioside concentrations in atherosclerotic patients are higher than in normal individuals (Lipids, 1994, 29(1), 1-5). Tissue derived from the kidneys of patients with polycystic kidney disease contains high levels of both glucosylceramide and lactosylceramide (J. Lipid. Res., 1996, Jun, 37(6), 1334-44). Renal hypertrophy in an animal model of diabetes is associated with increases in glycolipid synthesis, (J. Clin. Invest., 1993, Mar, 91(3), 797-803).

Glycolipid metabolism also plays a critical role in other neuronal disorders, such as Alzheimer's disease and epilepsy. For instance, Niemann-Pick C (NPC) patient neurons present with fibrillar tangles reminiscent of the morphology seen in Alzheimer's disease.

Interestingly, GM1 ganglioside binding by amyloid beta-protein induces conformational changes that support its formation of fibrous polymers, and the fibrillar deposition of this protein is an early event in Alzheimer's disease (Yanagisawa et al, (1995), Nat. Med. 1, 1062-6; Choo-Smith et al, (1997), Biol. Chem., 272, 22987-90). Thus, decreasing GM1 synthesis with agents such as NB-DNJ could inhibit the fibre formation seen in Alzheimer's disease.

In contrast, preliminary clinical trials have shown that neurodegenerative processes seen with Parkinson's disease, stroke and spinal cord injuries seem to improve by treating patients with GM1 ganglioside (Alter, (1998), Ann. NY Acad. Sci. 845, 391-4011; Schneider, (1998), Ann. NY. Acad. Sci., 845, 363-73; Geisler, (1998), Ann. NY. Acad. Sci., 845, 374-81). It is possible that co-administering glucosylceramide synthesis inhibitors would provide the clinician greater control over this treatment course. Inhibitors like NB-DNJ would limit

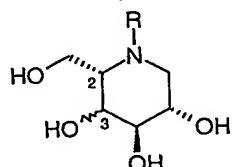
patient-specific inconsistencies by blocking their neuronal glycolipid synthesis. In addition, inhibiting glucosylceramide synthesis would limit the metabolism of administered glycolipids into other, perhaps unproductive, forms. Thus, the ability to modulate glucosylceramide synthesis with inhibitors such as NB-DNJ may be useful in treatment of a wide variety of 5 neuronal disorders.

It has also been shown that imino sugars can reversibly induce male sterility and can therefore be used as male contraceptives.

PCT/GB02/00106 discusses the prior art and discloses other piperidine derivatives useful as GCS inhibitors.

Given the importance of GCS in a wide spectrum of basic and applied science 10 interests, it is essential that new tools that provide a means for modulating this enzyme's function be developed. Towards this end, we have synthesized a number of novel compounds that are useful in inhibiting GCS's catalytic activity.

According to the invention there is provided a compound of formula (I) or a 15 pharmaceutically acceptable salt or prodrug thereof:



(I)

wherein

20 R is C_{1-3} alkylaryl where aryl is phenyl or pyridyl, wherein phenyl is substituted by one or more substituents selected from CN, $CONR^1_2$, SO_2R^2 , $N(R^2)_2$, and $N(R^1)COR^2$, or two adjacent substituents on the phenyl may together form a fused 5- or 6-membered saturated or unsaturated ring optionally containing 1 or 2 heteroatoms, selected from N and O, and the phenyl is optionally substituted by one or more additional substituents selected from F, Cl, Br, CF_3 , OCF_3 , and OR^1 ; and wherein pyridyl is substituted by one or more substituents, selected from, CN, $CONR^1_2$, SO_2R^2 , $N(R^2)_2$, $N(R^1)COR^2$, F, Cl, Br, CF_3 , OCF_3 , and OR^1 or two 25 adjacent substituents on the pyridyl may together form a fused 5- or 6-membered saturated or unsaturated ring which may optionally contain 1 or 2 heteroatoms, selected from N and O;

R^1 is H, or C_{1-6} alkyl; and

30 R^2 is C_{1-6} alkyl.

The hydroxyl group at position 3 may be fixed in either the R or the S configuration. The hydroxyl group at position 3 is preferably in the R configuration, i.e. the compound of formula (I) has the stereochemistry (2S,3R,4R,5S).

35 Preferably, the substituents on the aryl group are on one or more of the 3, 4 or 5 positions.

R is preferably C_1 alkylaryl where aryl is phenyl or pyridyl, wherein phenyl is substituted by one or more substituents selected from CN, $CONR^1_2$, SO_2R^2 , $N(R^2)_2$, and $N(R^1)COR^2$, or two adjacent substituents on the phenyl may together form a fused 5- or 6-membered saturated or unsaturated ring optionally containing 1 or 2 heteroatoms, selected from N and O, and the phenyl is optionally substituted by one or more additional substituents selected from F, Cl, Br, CF_3 , OCF_3 , and OR^1 ; and wherein pyridyl is substituted by one or 40

more substituents, selected from, CN, CONR¹, SO₂R², N(R²)₂, N(R¹)COR², F, Cl, Br, CF₃, OCF₃, and OR¹ or two adjacent substituents on the pyridyl may together form a fused 5- or 6-membered saturated or unsaturated ring which may optionally contain 1 or 2 heteroatoms, selected from N and O.

5 The compounds for use in the methods of the invention preferably have a molecular weight of less than 800, more preferably less than 600.

As described herein, the compounds of the present invention can be used for the inhibition of GCS. Thus, an aspect of the present invention provides the use of the compounds of formula (I) in medicine.

10 Suitable, pharmaceutically acceptable salts of the compounds of formula (I) include, but are not limited to, salts with inorganic acids such as hydrochloride, sulfate, phosphate, diphosphate, hydrobromide, and nitrate, or salts with an organic acid such as malate, maleate, fumarate, tartrate, succinate, citrate, acetate, lactate, methanesulfonate, p-toluenesulfonate, palmitate, salicylate, and stearate.

15 Suitable prodrugs of the compounds of formula (I) include, but are not limited to, pharmaceutically acceptable esters such as C₁₋₆ alkyl esters.

Some of the compounds of this invention may be crystallised or recrystallised from solvents such as aqueous and organic solvents. In such cases solvates may be formed. This invention includes within its scope stoichiometric solvates including hydrates as well as 20 compounds containing variable amounts of water that may be produced by processes such as lyophilisation.

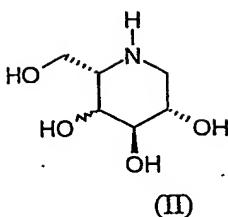
25 Certain of the compounds of formula (I) may exist in the form of optical isomers, e.g. diastereoisomers and mixtures of isomers in all ratios, e.g. racemic mixtures. The invention includes all such forms, in particular the pure isomeric forms. The different isomeric forms may be separated or resolved one from the other by conventional methods, or any given isomer may be obtained by conventional synthetic methods or by stereospecific or asymmetric syntheses.

Since the compounds of formula (I) are intended for use in pharmaceutical compositions it will readily be understood that they are each preferably provided in 30 substantially pure form, for example at least 60% pure, more suitably at least 75% pure and preferably at least 85%, especially at least 98% pure (% are on a weight for weight basis). Impure preparations of the compounds may be used for preparing the more pure forms used in the pharmaceutical compositions; these less pure preparations of the compounds should contain at least 1%, more suitably at least 5% and preferably from 10 to 59% of a compound 35 of the formula (I) or pharmaceutically acceptable derivative thereof.

The term "alkyl" as used herein whether on its own or as part of a larger group e.g. "alkylaryl", includes both straight and branched chain radicals. The term alkyl also includes those radicals wherein one or more hydrogen atoms are replaced by fluorine.

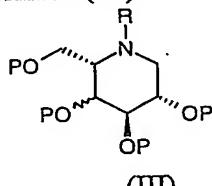
40 The compounds of formula (I) can be prepared by art-recognized procedures from known or commercially available starting materials. If the starting materials are unavailable from a commercial source, their synthesis is described herein, or they can be prepared by procedures known in the art.

Specifically, the compounds of formula (I) may be prepared by processes comprising:
 (a) reacting a compound of formula (II):



5 with NaBH_3CN and an aldehyde of formula R^2CHO in acetic acid-methanol, or with $\text{NaBH}(\text{OAc})_3$ and an aldehyde of formula R^2CHO in a solvent such as dichloromethane; wherein R^2 is C_{0-2} alkylaryl where aryl is as defined in formula (I); or

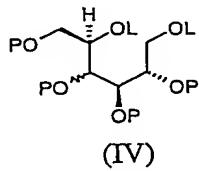
(b) deprotection of a compound of formula (III):



10 wherein R is as defined in formula (I), and P, which may be the same or different, are hydroxy protecting groups e.g. benzyl (Bn). When P is CH_2Ph the deprotection is conducted in the presence of hydrogen gas and a catalyst such as PdCl_2 or palladium on carbon in a suitable solvent such as an alcohol, e.g. ethanol. It will be understood that when P is CH_2Ph and R is CH_2Ph the R group can also be removed under these conditions to give compounds 15 of formula (II) thus compounds of formula (I) where R is CH_2Ph are preferably produced using process a) above.

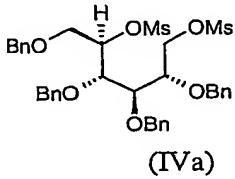
The compounds of formula (II) are known, see e.g. Carbohydr. Res., 1993, 246, 377-81 (2S3R4R5S) and Tet. Lett., 1997, 38(45), 8009-12 (2S3S4R5S).

20 Compounds of formula (III) may be prepared by reacting a compound of formula (IV):

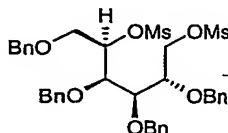


25 wherein L, which may be the same or different are leaving groups, such as mesyl, and P is as defined for formula (III), with an amine of formula RNH_2 , wherein R is as defined in formula (I), either neat or in a solvent such as tetrahydrofuran.

Compound (IVa), wherein L is mesyl and P is benzyl, is a known compound: V.S. Rao et al., Can. J. Chem., (1981), 59(2), 333-8; P.A. Fowler et al., Carbohydr. Res., (1993), 246, 377-81.



Compound (IVb), wherein L is mesyl and P is benzyl, may be prepared by reacting 2,3,4,6-tetra-O-benzyl-D-galactitol with mesyl chloride in the presence of a base such as pyridine.



5

(IVb)

Any novel intermediate compounds as described herein also fall within the scope of the present invention.

Thus according to a further aspect of the invention there is provided a compound of formula (III) as defined above.

During the synthesis of the compounds of formula (I) labile functional groups in the intermediate compounds, e.g. hydroxy, carboxy and amino groups, may be protected. A comprehensive discussion of the ways in which various labile functional groups may be protected and methods for cleaving the resulting protected derivatives is given in for example *Protective Groups in Organic Chemistry*, T.W. Greene and P.G.M. Wuts, (Wiley-Interscience, New York, 2nd edition, 1991).

The compounds of formula (I) may be prepared singly or as compound libraries comprising at least 2, for example 5 to 500 compounds, and more preferably 10 to 100 compounds of formula (I). Libraries of compounds of formula (I) may be prepared by a combinatorial 'split and mix' approach or by multiple parallel synthesis using either solution phase or solid phase chemistry, by procedures known to those skilled in the art.

Thus according to a further aspect of the invention there is provided a compound library comprising at least 2 compounds of formula (I) or pharmaceutically acceptable salts thereof.

The pharmaceutically effective compounds of formula (I) and pharmaceutically acceptable salts thereof, may be administered in conventional dosage forms prepared by combining a compound of formula (I) ("active ingredient") with standard pharmaceutical carriers or diluents according to conventional procedures well known in the art. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation.

According to a further aspect the present invention provides pharmaceutical formulations comprising one or more compounds of formula (I), together with one or more pharmaceutically acceptable carriers or excipients.

The pharmaceutical compositions of the invention may be formulated for administration by any route, and include those in a form adapted for oral, topical or parenteral administration to mammals including humans.

Pharmaceutical formulations may be adapted for administration by any appropriate route, for example by the oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual or transdermal), vaginal or parenteral (including subcutaneous, intramuscular, intravenous or intradermal) route. Such formulations may be prepared by any method known in the art of pharmacy, for example by bringing into association the active ingredient with the carrier(s) or excipient(s).

Pharmaceutical formulations adapted for oral administration may be presented as discrete units such as capsules or tablets; powders or granules; solutions or suspensions in aqueous or non-aqueous liquids; edible foams or whips; or oil-in-water liquid emulsions or water-in-oil liquid emulsions.

5 Pharmaceutical formulations adapted for transdermal administration may be presented as discrete patches intended to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. For example, the active ingredient may be delivered from the patch by iontophoresis as generally described in *Pharmaceutical Research*, 3(6), 318, (1986).

10 Pharmaceutical formulations adapted for topical administration may be formulated as ointments, creams, suspensions, lotions, powders, solutions, pastes, gels, impregnated dressings, sprays, aerosols or oils and may contain appropriate conventional additives such as preservatives, solvents to assist drug penetration and emollients in ointments and creams.

15 For applications to the eye or other external tissues, for example the mouth and skin, the formulations are preferably applied as a topical ointment or cream. When formulated in an ointment, the active ingredient may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredient may be formulated in a cream with an oil-in-water cream base or a water-in-oil base.

20 Pharmaceutical formulations adapted for topical administration to the eye include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent.

Pharmaceutical formulations adapted for topical administration in the mouth include lozenges, pastilles and mouth washes.

25 Pharmaceutical formulations adapted for rectal administration may be presented as suppositories or enemas.

30 Pharmaceutical formulations adapted for nasal administration wherein the carrier is a solid include a coarse powder having a particle size for example in the range 20 to 500 microns which is administered in the manner in which snuff is taken, i.e. by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable formulations wherein the carrier is a liquid, for administration as a nasal spray or as nasal drops, include aqueous or oil solutions of the active ingredient.

35 Pharmaceutical formulations adapted for administration by inhalation include fine particle dusts or mists which may be generated by means of various types of metered dose pressurised aerosols, nebulizers or insufflators.

40 Pharmaceutical formulations adapted for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations.

Pharmaceutical formulations adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and

thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations may also include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavouring agents.

5 The pharmaceutical formulations according to the invention are preferably adapted for oral administration.

10 The formulations may also contain compatible conventional carriers, such as cream or ointment bases and ethanol or oleyl alcohol for lotions. Such carriers may be present as from about 1% up to about 98% of the formulation. More usually they will form up to about 80% of the formulation.

15 Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants, for example potato starch; or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with 20 water or other suitable vehicle before use. Such liquid preparations may contain conventional additives, such as suspending agents, for example sorbitol, methyl cellulose, glucose syrup, gelatin, hydroxyethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, oily 25 esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl *p*-hydroxybenzoate or sorbic acid, and, if desired, conventional flavouring or colouring agents.

Suppositories will contain conventional suppository bases, e.g. cocoa-butter or other glyceride.

30 For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, water being preferred. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the compound can be dissolved in water for injection and filter sterilised before filling into a suitable vial or ampoule and sealing.

35 Advantageously, agents such as a local anaesthetic, preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. The dry lyophilized powder is then sealed in the vial and an accompanying vial of water for injection may be supplied to reconstitute the liquid prior to use. Parenteral suspensions are prepared in substantially the 40 same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilization cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The compositions may contain from 0.1% by weight, preferably from 10-60% by weight, of the active material, depending on the method of administration.

Pharmaceutical formulations may be presented in unit dose forms containing a predetermined amount of active ingredient per dose. Such a unit may contain for example up to 5 1g, suitably 10mg to 600mg, preferably 50mg to 300mg and more preferably 50mg to 150mg depending on the condition being treated, the route of administration and the age, weight and condition of the patient. Preferred unit dosage formulations are those containing a daily dose or sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient.

It will be recognized by one of skill in the art that the optimal quantity and spacing of 10 individual dosages of a formula (I) compound will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular mammal being treated, and that such optimums can be determined by conventional techniques. It will also be appreciated by one of skill in the art that the optimal course of treatment, i.e., the number of doses of the formula (I) compound given per day for a defined 15 number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

No toxicological effects are indicated when a compound of formula (I) or a pharmaceutically acceptable derivative thereof is administered in the above-mentioned dosage range.

20 The compounds of the present invention are useful in that they are capable of inhibiting glucosylceramide synthase. Thus, the compounds of the invention can be used in the treatment of various glycolipid storage diseases such as Gaucher's disease, Sandhoff's disease, Tay-Sachs disease, Fabry disease, GM1 gangliosidosis etc. In addition, compounds such as this also can find use in the treatment of conditions in which glycolipid accumulation occurs such as Niemann-Pick 25 disease, mucopolysaccharidoses (MPS I, MPS IIIA, MPS IIIB, MPS VI and MPS VII), mucolipidosis type IV and α -mannosidosis.

The compounds of the present invention can also be used in the treatment of cancers in which glycolipid synthesis is abnormal such as brain tumours, neuroblastoma, malignant melanoma, renal adenocarcinoma and multi-drug resistant cancers in general.

30 The compounds of the present invention can also be used in the treatment of disease caused by infectious organisms which use cell surface glycolipid as receptors for the infectious organism or toxin produced by the infectious organism.

35 The compounds of the present invention can also be used in the treatment of disease caused by infectious organisms for which the synthesis of glucosylceramide is an essential or important process such as the pathogenic fungus cryptococcus neoformans.

The compounds of the present invention can also be used in the treatment of disease in which excessive glycolipid synthesis occurs such as but not limited to, atherosclerosis, polycystic kidney disease and diabetic renal hypertrophy.

40 The compounds of the present invention can also be used in the treatment of neuronal disorders, such as Alzheimer's disease and epilepsy; and neuronal degenerative disease such as Parkinsons' disease

The compounds of the present invention can also be used in the treatment of neuronal injury such as spinal cord injuries or stroke.

The compounds of the present invention can also be used for reversibly rendering a male mammal infertile.

The compounds of the present invention can also be used in the treatment of obesity.

In additional aspects, therefore, the present invention provides:

- 5 (i) the use of a compound of formula (I) as an inhibitor of glucosylceramide synthase.
- (ii) the use of a compound of formula (I) in the manufacture of a medicament for the treatment of a glycolipid storage disease. Examples of glycolipid storage disease which can be treated include, but are not limited to: Gaucher disease, Sandhoff's disease, Tay-Sachs disease, Fabry disease or GM1 gangliosidosis.
- 10 (iii) the use of a compound of formula (I) in the manufacture of a medicament for the treatment of Niemann-Pick disease types A and C.
- (iv) the use of a compound of formula (I) in the manufacture of a medicament for the treatment of mucopolysaccharidosis type I, mucopolysaccharidosis type IIID, mucopolysaccharidosis type IIIA, mucopolysaccharidosis type VI or mucopolysaccharidosis type VII.
- 15 (v) the use of a compound of formula (I) in the manufacture of a medicament for the treatment of α -mannosidosis or mucolipidosis type IV.
- (vi) the use of a compound of formula (I) in the manufacture of a medicament for the treatment of cancers in which glycolipid synthesis is abnormal, including but not limited to neuronal cancer including neuroblastoma, brain cancer, renal adenocarcinoma, malignant melanoma, multiple myeloma and multi-drug resistant cancers.
- 20 (vii) the use of a compound of formula (I) in the manufacture of a medicament for use in the treatment of Alzheimer's disease, epilepsy or stroke.
- (viii) the use of a compound of formula (I) in the manufacture of a medicament for use in the treatment of Parkinson's disease.
- 25 (ix) the use of the compound of formula (I) in the manufacture of a medicament in the treatment of spinal injury.
- (x) the use of a compound of formula (I) in the manufacture of a medicament for use in the treatment of disease caused by infectious microorganisms which utilize glycolipids on the 30 surface of cells as receptors for the organism itself or toxins produced by the organism.
- (xi) the use of a compound of formula (I) in the manufacture of a medicament for use in the treatment of disease caused by infectious organisms for which the synthesis of glucosylceramide is an essential or important process such as but not limited to pathologies associated with infections of the pathogenic fungus cryptococcus neoformans.
- 35 (xii) the use of a compound of formula (I) in the manufacture of a medicament for use in the treatment of diseases associated with abnormal glycolipid synthesis including but not limited to polycystic kidney disease, diabetic renal hypertrophy and atherosclerosis.
- (xiii) the use of a compound of formula (I) in the manufacture of a medicament for the treatment of a condition treatable by the administration of a ganglioside such as GM1 40 ganglioside. Examples of such conditions are Parkinson's disease, stroke and spinal cord injuries.
- (xiv) the use of a compound of formula (I) in the manufacture of a medicament for reversibly rendering a male mammal infertile.

(xv) the use of a compound of formula (I) in the manufacture of a medicament for the treatment of obesity, e.g. as an appetite suppressant.

(xvi) a method for the treatment of a glycolipid storage disease, e.g. Gaucher's disease, Sandhoff's disease, Tay-Sachs disease or GM1 gangliosidosis, which comprises the step of 5 administering to a patient an effective amount of a compound of formula (I).

(xvii) a method for the treatment of Niemann-Pick disease types A and C, which comprises the step of administering to a patient an effective amount of a compound of formula (I).

(xviii) a method for the treatment of mucopolysaccharidosis type I, 10 mucopolysaccharidosis type IIID, mucopolysaccharidosis type IIIA, mucopolysaccharidosis type VI or mucopolysaccharidosis type VII which comprises the step of administering to a patient an effective amount of a compound of formula (I).

(xix) a method for the treatment of α -mannosidosis or mucolipidosis type IV which comprises the step of administering to a patient an effective amount of a compound of formula 15 (I).

(xx) a method for the treatment of cancers in which glycolipid synthesis is abnormal, including but not limited to neuronal cancer including neuroblastoma, brain cancer, renal adenocarcinoma, malignant melanoma, multiple myeloma and multi-drug resistant cancers which comprises the step of administering to a patient an effective amount of a compound of 20 formula (I).

(xxi) a method for the treatment of Alzheimer's disease, epilepsy or stroke which comprises the step of administering to a patient an effective amount of a compound of formula (I).

(xxii) a method for the treatment of Parkinson's disease, which comprises the step of 25 administering to a patient an effective amount of a compound of formula (I).

(xxiii) a method for the treatment of spinal injury which comprises the step of administering to a patient an effective amount of a compound of formula (I).

(xxiv) a method for the treatment of disease caused by infectious microorganisms which utilize glycolipids on the surface of cells as receptors for the organism itself or toxins 30 produced by the organism which comprises the step of administering to a patient an effective amount of a compound of formula (I).

(xxv) a method for the treatment of disease caused by infectious organisms for which the synthesis of glucosylceramide is an essential or important process such as but not limited to pathologies associated with infections of the pathogenic fungus cryptococcus neoformans which 35 comprises the step of administering to a patient an effective amount of a compound of formula (I).

(xxvi) a method for the treatment of diseases associated with abnormal glycolipid synthesis including but not limited to polycystic kidney disease, diabetic renal hypertrophy and atherosclerosis, which comprises the step of administering to a patient an effective amount of a 40 compound of formula (I).

(xxvii) a method for the treatment of a condition treatable by the administration of a ganglioside such as GM1 ganglioside, which comprises the step of administering to a patient an effective amount of a compound of formula (I). Examples of such conditions are Parkinson's disease, stroke and spinal cord injuries.

(xxviii) a method for reversibly rendering a male mammal infertile, which comprises the step of administering to said male mammal an effective amount of a compound of formula (I).

(xxix) a method for the treatment of obesity, which comprises the step of administering to a patient an effective amount of a compound of formula (I).

5 The invention also provides for the use of a compound of formula (I) for the treatment of the above mentioned diseases and conditions.

All publications, including, but not limited to, patents and patent applications, cited in this specification, are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set

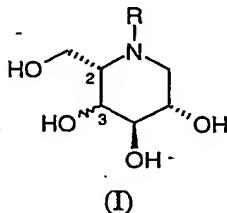
10 forth.

The compounds of the invention can be assayed to determine their IC₅₀ concentrations. The assay for inhibition of GCS is described in Platt et al, J.Biol.Chem., (1994), 269, 27108, the enzyme source being human recombinant GCS expressed in insect cells. For comparison, glucosidase and mannosidase assays are described in (Biochemical Genetics, A Laboratory Manual, Oxford University

15 Press).

CLAIMS:

1. A compound of formula (I) or a pharmaceutically acceptable salt or prodrug thereof:



wherein

R is C_{1-3} alkylaryl where aryl is phenyl or pyridyl, wherein phenyl is substituted by one or more substituents selected from CN, $CONR^1_2$, SO_2R^2 , $N(R^2)_2$, and $N(R^1)COR^2$ or two adjacent substituents on the phenyl may together form a fused 5- or 6-membered saturated or unsaturated ring optionally containing 1 or 2 heteroatoms, selected from N and O, and the phenyl is optionally substituted by one or more additional substituents selected from F, Cl, Br, CF_3 , OCF_3 , and OR^1 ; and wherein pyridyl is substituted by one or more substituents, selected from, CN, $CONR^1_2$, SO_2R^2 , $N(R^2)_2$, $N(R^1)COR^2$, F, Cl, Br, CF_3 , OCF_3 , and OR^1 or two adjacent substituents on the pyridyl may together form a fused 5- or 6-membered saturated or unsaturated ring which may optionally contain 1 or 2 heteroatoms, selected from N and O;

R^1 is H, or C_{1-6} alkyl; and

R^2 is C_{1-6} alkyl.

20 2. A compound as defined in claim 1 wherein the hydroxyl group at position 3 is in the R configuration.

3. A compound as defined in claim 1 or 2 wherein R is C_1 alkylaryl where aryl is phenyl or pyridyl, wherein phenyl is substituted by one or more substituents selected from CN, $CONR^1_2$, SO_2R^2 , $N(R^2)_2$, and $N(R^1)COR^2$ or two adjacent substituents on the phenyl may together form a fused 5- or 6-membered saturated or unsaturated ring optionally containing 1 or 2 heteroatoms, selected from N and O, and the phenyl is optionally substituted by one or more additional substituents selected from F, Cl, Br, CF_3 , OCF_3 , and OR^1 ; and wherein pyridyl is substituted by one or more substituents, selected from, CN, $CONR^1_2$, SO_2R^2 , $N(R^2)_2$, $N(R^1)COR^2$, F, Cl, Br, CF_3 , OCF_3 , and OR^1 or two adjacent substituents on the pyridyl may together form a fused 5- or 6-membered saturated or unsaturated ring which may optionally contain 1 or 2 heteroatoms, selected from N and O.

35 4. A compound as defined in any one of claims 1 to 3 where the substituents on the aryl are on one or more of the 3, 4, or 5 positions.

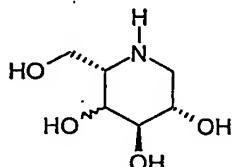
5. A compound as defined in any one of the preceding claims for use in medicine.

40 6. A pharmaceutical formulation comprising at least one compound as defined in any one of claims 1 to 4, optionally together with one or more pharmaceutically acceptable carriers, excipients and/or diluents.

7. A process for the preparation of a compound as defined in any one of claims 1 to 4 which comprises:

a) reacting a compound of formula (II):

5

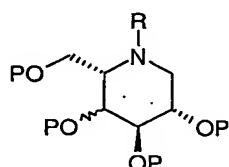


(II)

with NaBH_3CN and an aldehyde of formula R^2CHO in acetic acid-methanol, or with $\text{NaBH}(\text{OAc})_3$ and an aldehyde of formula R^2CHO in a solvent; wherein R^2 is C_{0-2} alkylaryl

10 where aryl is as defined in formula (I); or

b) deprotection of a compound of formula (III):



(III)

15 wherein R is as defined in claim 1, and P, which may be the same or different, are hydroxy protecting groups.

8. The use of a compound as defined in any one of claims 1 to 4 in the manufacture of an inhibitor of glucosylceramide synthase.

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9. The use of a compound as defined in any one of claims 1 to 4 in the manufacture of a medicament for the treatment of a glycolipid storage disease.

25 10. The use as claimed in claim 9 wherein the glycolipid storage disease is Gaucher disease, Sandhoffs disease, Tay-Sachs disease, Fabry disease or GM1 gangliosidosis.

11. The use of a compound as defined in any one of claims 1 to 4, in the manufacture of a medicament for the treatment of Niemann-Pick disease type C, mucopolysaccharidosis type I, mucopolysaccharidosis type IIID, mucopolysaccharidosis type IIIA, mucopolysaccharidosis type VI, mucopolysaccharidosis type VII, α -mannosidosis or mucolipidosis type IV.

30 12. The use of a compound as defined in any one of claims 1 to 4, in the manufacture of a medicament for the treatment of neuronal cancer including neuroblastoma, brain cancer, renal adenocarcinoma, malignant melanoma, multiple myeloma and multi-drug resistant cancers.

13. The use of a compound as defined in any one of claims 1 to 4, in the manufacture of a medicament for use in the treatment of Alzheimer's disease, epilepsy, stroke, Parkinson's disease or spinal injury.

5 14. The use of a compound as defined in any one of claims 1 to 4, in the manufacture of a medicament for use in the treatment of disease caused by infectious microorganisms which utilize glycolipids on the surface of cells as receptors for the organism itself or toxins produced by the organism or disease caused by infectious organisms for which the synthesis of glucosylceramide is an essential or important process.

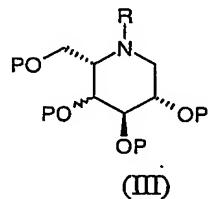
10 15. The use of a compound as defined in any one of claims 1 to 4, in the manufacture of a medicament for use in the treatment of diseases associated with abnormal glycolipid synthesis, e.g. polycystic kidney disease, diabetic renal hypertrophy and atherosclerosis.

15 16. The use of a compound as defined in any one of claims 1 to 4, in the manufacture of a medicament for the treatment of a condition treatable by the administration of a ganglioside such as GM1 ganglioside.

20 17. The use of a compound as defined in any one of claims 1 to 4, in the manufacture of a medicament for use in reversibly rendering a male mammal infertile.

18. The use of a compound as defined in any one of claims 1 to 4, in the manufacture of a medicament for the treatment of obesity.

25 19. A compound of formula (III):



wherein R is as defined in claim 1, and P, which may be the same or different, are hydroxy protecting groups.